When Guidelines Don't Help, How Do I 'Roll The Dice' On My Patients?

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Disclosures

Dr. Einstein has advised, but does not receive an honorarium from any companies. In specific cases his employer has received payment for his consultation from Photocure, Papivax, Inovio, Cynvec, PDS Biotechnologies, Natera, and Immunovaccine. If travel is required for meetings with any industry, the company pays for Dr. Einstein's travel-related expenses. Also, his employers have received grant funding for research related costs of clinical trials that Dr. Einstein has been the overall PI or local PI for the past 12 months from Astra Zeneca, Baxalta, Pfizer, Inovio, Fujiboro, Eli Lilly.

Objectives

- Assist clinicians to interpret evidence, guidelines, and make sense of a growing body of additional tests to be able to individualize management when algorithms don't necessarily apply
- Interpreting cervical cancer screening tests to help you help your patients

Why abnormal screening tests might not fit into algorithms

- In the US, cervical cancer screening is based on cytology and HPV testing and when abnormal, histology, which can include other molecular tests (eg p16/Ki-67, E6/E7)
- Rare outcomes that do not allow even large datasets to inform risk and counseling
- Testing timing might not be exactly as directed by guidelines. Some too often and some too infrequent
- New tests that have limited data and limited guidance

Einstein MH. Up To Date HPV testing of the cervix: Management of Abnormal Results. https://www.uptodate.com/contents/human-papillomavirus-testing-of-the-cervix-management-of-abnormal-results?search=mark%20einstein%20and%20hpv&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=5

Why abnormal screening tests might not fit into algorithms

- Clinicians might find the abundance of clinical data difficult to interpret and this makes it hard to choose the next appropriate management step
- Objective: Assist clinicians in interpreting evidence, guidelines, and make sense of a growing body of additional tests to be able to individualize management when algorithms are not useful

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Rationale for evaluation strategies

- Equal management of equal risks
  - Data for rare outcomes limited so risk calculations for those cannot be made with certainty
- Next steps include:
  1) Continued routine screening
  2) Active surveillance (more frequent and/or additional tests)
  3) Colposcopy
  4) Treatment

Katki HA et al. JLGTD 2013

Straightforward approach to evaluating cytology and HPV testing results

- Cytology is a marker for CURRENT risk of clinically relevant disease
- HPV testing is an excellent marker for FUTURE risk of clinically relevant disease
  - HPV testing provides current risk as well, especially genotyping, but with low specificity
- In clinical decision-making, knowledge of past or present HPV results or persistence, defined as two or more positive HPV tests 12 months or more apart, can better inform decisions
  - Testing for 16 and 18, positive or negative, can also better inform decisions

Massad LS et al. JLGTD 2013
Einstein MH and Burk RD Papillomavirus Report 2001

Groups of women with HPV positive results

- Found from cotesting women ages 30-64
- Found from ASCUS reflex in women 21-64
  - New infections common in women under age 25, but clinically relevant disease in these women is uncommon
- Found from unindicated testing
- Categories of HPV infection 1) first ever result, 2) persistent (recurring) result, 3) new after previously reverting to negative

First HPV positive result

- If young, conservative management since most will revert to a negative result within 6-12 months
- ‘Older’ requires identifying if new or persistent through active surveillance and repeat testing at short interval

HPV positive result with negative cytology

- If 16/18+, colposcopy
- If not 16/18+, active surveillance in shorter interval which might include cotesting or HPV genotyping

Recurrent HPV positive result

- Often cytology is new low grade or ASCUS
- Reactivation of a latent infection
  - Impossible to prove if new or reactivation
  - Most likely reactivation of prior infections[1,2]
- Occasionally positive and occasionally negative
  - Active surveillance as this might be persistent

1. Markt SC JID 2012
2. Castle PE JID 2005

Persistent HPV positive result

- Defined as consecutively positive HPV results at least 12 months apart[1]
- Most, if not all, will become CIN 2+ over 5-7 years if results remain persistent[2]
  - All should have active surveillance
  - Often persistent LSIL
- If improvement over time, chances are almost zero the patient will develop CIN 2+ in time[2]

1. Einstein MH. Papillomavirus Report 2001
2. Elfgren K. Am J Obstet Gynecol 2017

Persistent HPV positive, low-risk cytology, negative colposcopy

- FRUSTRATING (for both provider and patient)
- Perform thorough vaginal colposcopy
- No currently available markers to improve identification of clinically concerning patients, so active surveillance

Genotyping positive

HPV 16 and/or 18

- Immediate triage to colposcopy
- Risks of CIN 2+ with these results far exceeds threshold to colposcopy regardless of cytology result

Oncogenic HPV positive, not 16/18

- If cytology warrants colposcopy, triage to colposcopy
- Otherwise active surveillance

HPV-Negative Cytology Unsatisfactory

- Cervical cytology must be repeated even if result is also HPV negative
- Unsatisfactory result considered unreliable for evaluation and scant cellularity may result in a false negative result

Other tests that are available or on the horizon

- p16INK4a/Ki-67 is a proliferative marker associated with CIN 2+
  - Used for IHC for diagnosis[1]
  - Used in cytology it appears more sensitive than a Pap alone[2]
- Tests for expression of E6/E7 mRNA, which is highly correlated with CIN 2+[3,4]

1. Darragh TM. JLGTD 2012
2. Wright TC. Gynecol Oncol 2017
3. Alaghehbandan R. Diagn Cytopathol 2013
4. Rikaart DC. J Clin Microbiol 2012